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blood advances

Outcomes of a clinician-directed protocol for discontinuation of complement inhibition therapy in atypical hemolytic uremic syndrome

Shruti Chaturvedi,[1] Noor Dhaliwal,[2] Sarah Hussain,[1] Kathryn Dane,[3] Harshvardhan Upreti,[2] Evan M. Braunstein,[1] Xuan Yuan,[1] C. John Sperati,[4] Alison R. Moliterno,[1] and Robert A. Brodsky[1]

[1]Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Maulana Azad Medical College, University of Delhi, Delhi, India; and [3]Department of Pharmacy and [4]Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD

Key Points

- Eculizumab discontinuation with close monitoring is safe in most patients with aHUS.
- *CFH* and *MCP* variants may be associated with higher risk of relapse, which needs to be evaluated in larger, multicenter studies.

Terminal complement inhibition is the standard of care for atypical hemolytic uremic syndrome (aHUS). The optimal duration of complement inhibition is unknown, although indefinite therapy is common. Here, we present the outcomes of a physician-directed eculizumab discontinuation and monitoring protocol in a prospective cohort of 31 patients that started eculizumab for acute aHUS (and without a history of renal transplant). Twenty-five (80.6%) discontinued eculizumab therapy after a median duration on therapy of 2.37 (interquartile range: 1.06, 9.70) months. Eighteen patients discontinued per protocol and 7 because of nonadherence. Of these, 5 (20%) relapsed; however, relapse rate was higher in the case of nonadherence (42.8%) vs clinician-directed discontinuation and monitoring (11.1%). Four of 5 patients who relapsed were successfully retreated without a decline in renal function. One patient died because of recurrent aHUS and hypertensive emergency in the setting of nonadherence. Nonadherence to therapy (odds ratio, 8.25; 95% confidence interval, 1.02-66.19; $P = .047$) was associated with relapse, whereas the presence of complement gene variants (odds ratio, 1.39; 95% confidence interval, 0.39-4.87; $P = .598$) was not significantly associated with relapse. Relapse occurred in 40% (2 of 5) with a *CFH* or *MCP* variant, 33.3% (2 of 6) with other complement variants, and 0% (0 of 6) with no variants ($P = .217$). There was no decline in mean glomerular filtration rate from the date of stopping eculizumab until end of follow-up. In summary, eculizumab discontinuation with close monitoring is safe in most patients, with low rates of aHUS relapse and effective salvage with eculizumab retreatment in the event of recurrence.

Introduction

Atypical hemolytic uremic syndrome (aHUS) is an acute, life-threatening disorder caused by complement dysregulation leading to a thrombotic microangiopathy (TMA) and end organ dysfunction, predominantly affecting the renal circulation. Up to 50% to 70% of patients have mutations in complement regulation genes.[1,2] In the pre-eculizumab era, 56% of patients with aHUS progressed to end-stage renal disease within the first year.[3] Eculizumab, an anti-C5 monoclonal antibody, is highly effective in treating aHUS and leads to rapid and sustained improvement in hematologic parameters and renal function.[1,4,5] Indefinite therapy with eculizumab is currently the standard of care for patients with aHUS. Recently, a longer-acting C5 inhibitor ravulizumab was also approved for aHUS.[6] However, long-term complement inhibition therapy comes with an immense financial burden,[7] in addition to

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We did not generate large scale genomic data. However, all sequencing data of patient samples will be shared by contacting schatur3@jhmi.edu for original data pertaining for this manuscript. No identifiable data will be shared. Requests for de-identified data from internal or external investigators will be evaluated on an individual basis.

subjecting patients to a small but real risk of meningococcal infection[8] and the inconvenience of needing infusions every 2 weeks (eculizumab) or every 2 months (ravulizumab).

Advances in our understanding of aHUS also provide rationale for limited duration of complement inhibition therapy in aHUS. Penetrance of aHUS-associated complement mutations is low, and a strong complement amplifying trigger may be required for clinically apparent TMA to manifest.[2,3] Reports suggest that many patients with aHUS may safely discontinue eculizumab therapy.[9-16] Although a risk of relapse remains, most patients in these reports were successfully salvaged with timely retreatment without significant worsening of renal function. Our group has also previously described excellent results in 15 patients with aHUS who discontinued eculizumab therapy.[17] Here, we present a physician-directed eculizumab discontinuation and monitoring protocol and report an updated analysis of outcomes of eculizumab discontinuation in a prospective cohort of 32 patients with aHUS enrolled in the Johns Hopkins Complement Associated Disease Registry. We also examined clinical and genetic risk factors for relapse after discontinuing eculizumab therapy.

Methods

Patients and data collection

Consecutive patients with aHUS enrolled in the Johns Hopkins Complement Associated Disease Registry between January 2014 and June 2020 who initiated eculizumab therapy during an acute episode of complement-mediated TMA and had at least 3 months of follow-up were included in the study. Inclusion criteria included age $\geq$18 years and a diagnosis of acute aHUS based on the following criteria: (1) platelet count $<150 \times 10^9$/L, (2) serum creatinine >2.25 mg/dL, (3) schistocytes on peripheral blood smear and acute TMA on renal biopsy, if performed, (4) ADAMTS13 activity >10%, and (5) Shiga toxin negative. Criteria numbers 1 and 3 to 5 were required for diagnosis. Criteria 2 (serum creatinine >2.25 mg/dL) was considered supportive of the diagnosis but was not required, and patients with a lower serum creatinine could be included if otherwise consistent with aHUS. We included only patients who developed acute TMA with native kidneys and excluded those that started eculizumab in the peri-renal transplant setting for end-stage renal disease because of confirmed or presumed aHUS and those with a history of aHUS relapse, because discontinuation likely carries higher risk in these cases. We did not include patients that developed TMA associated with hematopoietic or solid organ transplantation. Patients were followed as clinically indicated, most commonly every 3 months, until death, or last clinical contact. Data regarding clinical presentation, laboratory studies, eculizumab therapy, and outcomes including death and renal function were collected as part of the registry. We collected results of clinical complement gene sequencing when available. We included any rare (minor allele frequency < 0.005) variants in *C3, CFB. CFH, CFI, CFHR5, MCP, DGKE, THBD,* and *PLG*. We did not include variants in *ADAMTS13*. We included homozygous (but not heterozygous) *CFHR1* deletion, although this is not a rare variant, based on strong association with aHUS and presence of factor H autoantibodies.[2,18-21] We also recorded the presence or absence of factor H autoantibodies. Pathogenic complement variants predispose to aHUS and can be considered risk factors for development of disease. Therefore, variants of undetermined significance were included in the analysis, especially because functional data are available for only a limited number of reported variants, and in silico prediction tools are not uniformly accurate. Data were collected and stored in RedCap, a secure, web-based, data management platform hosted at Johns Hopkins University. The institutional review board of the Johns Hopkins University School of Medicine approved this study. Study was conducted in accordance with the Declaration of Helsinki.

Hopkins protocol for eculizumab discontinuation and monitoring

Our eculizumab discontinuation and monitoring protocol is summarized in Figure 1. Guiding principles of this approach are that eculizumab discontinuation is considered if all of the following conditions are met: (1) no clinical evidence of ongoing thrombotic microangiopathy (platelets $<150 \times 10^9$/L, lactate dehydrogenase > 1.5 times the upper limit of normal, schistocytes on blood smear), (2) renal function returned to normal or plateaued at a new baseline for at least 3 months, (3) no active trigger (for patients that have an identified trigger) and C reactive protein levels may be obtained when it is unclear whether the trigger has resolved, (4) no organ transplantation for aHUS, and (5) patient adherent with follow-up and able to make an informed decision regarding the risks vs benefits of discontinuation. Eculizumab may be discontinued if all the conditions mentioned above are met. Eculizumab was continued (or switched to ravulizumab) even if all conditions were met but patient was unwilling to stop therapy. Of note, we do not follow a prescribed minimum duration of therapy unlike other protocols that may require a minimum duration of therapy such as 6 months.[16] Laboratory studies including complete blood count with peripheral smear, lactate dehydrogenase, serum creatinine, urinalysis, and urine protein/creatinine ratio are initially performed 2 weeks after the last eculizumab, then weekly for 1 month, every 2 weeks for 2 months, monthly for 3 months, and every 3 months thereafter. Patients are also encouraged to perform home urine dipstick testing for proteinuria and to monitor their blood pressure at home. Additional laboratory tests may be performed in case of acute illness, surgery, or pregnancy. Eculizumab (or ravulizumab if long-term therapy is anticipated) is restarted if relapse is suspected. Temporarily restarting eculizumab is also considered in high-risk situations such as acute severe illness, pregnancy, or major surgery. For patients that are likely to be on long-term (indefinite) therapy with a C5 inhibitor, including those that are not candidates for discontinuing treatment or those that need to restart therapy because of TMA recurrence, we preferentially switch to ravulizumab because of less frequent infusions and lower cost.

Data analysis

Data were summarized as counts and proportions for categorical variables and medians and interquartile ranges (IQR; or mean $\pm$ standard deviation) for continuous variables. The χ^2 test was used to compare relapse rate in different groups. We attempted to evaluate clinical and genetic risk factors for relapse; however, the small number of relapses precluded multivariable analysis. We evaluated the mean $\pm$ standard deviation change in estimated glomerular filtration rate (eGFR) (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) from date of stopping eculizumab until last follow-up using the paired samples *t* test and separately analyzed outcomes of patients who stopped

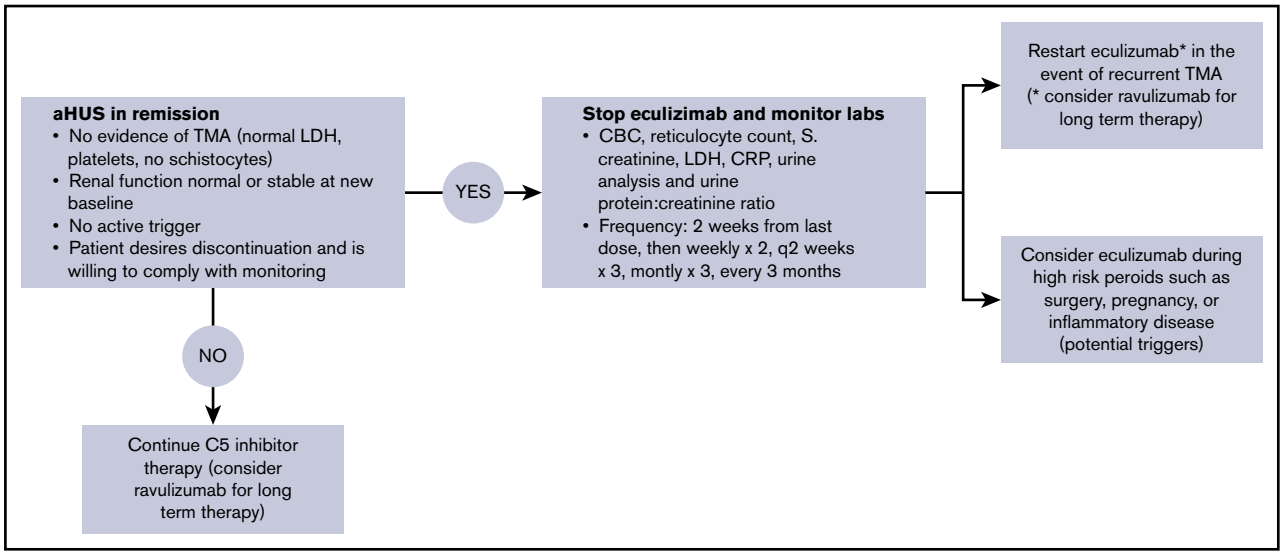

Figure 1. Protocol for eculizumab discontinuation and monitoring. All 4 of the following criteria must be met before we discontinue eculizumab: resolved TMA, renal function normal or stable at new baseline, no active trigger (in patients that had an identified trigger), and patients desire to stop therapy and agree to monitoring plan. Monitoring is conduced as outlined. Home urine dipstick monitoring may also be used as an adjunct. We restart a C5 inhibitor (eculizumab or ravulizumab) in the case of recurrent TMA, in which case therapy is continued indefinitely or possibly temporarily during high-risk periods such as pregnancy, surgery, or flare of inflammatory disease. When long-term therapy is anticipated, we suggest ravulizumab rather than eculizumab.

eculizumab on the physician-directed protocol vs nonadherence to therapy and relapsing vs nonrelapsing patients. $P < .05$ was considered significant. Stata version 15 (StataCorp.) was used for all analyses.

Results

Cohort characteristics

Between January 2011 and June 2020, 42 patients with aHUS received treatment with eculizumab at our institution during the study period. Of these, 10 received eculizumab in the perioperative setting for renal transplantation (because of end-stage renal disease attributed to prior aHUS) and were excluded from the analysis. Thirty-two patients received eculizumab for acute aHUS, of which 1 patient died during the acute aHUS episode. The 31 adult patients with aHUS who received treatment with eculizumab for acute TMA and had at least 3 months of follow-up are included in the analysis (Figure 2). Median age at initial diagnosis of aHUS was 44 (IQR: 25, 52) years, and 77.4% (24 of 31) were female. A putative trigger was identified for 67.7% (21 of 31) patients. Triggers included infections (N = 7), autoimmune disease flares (N = 4), pregnancy and cesarean section (N = 1), surgery (N = 1), cancer/chemotherapy (N = 4), and other inflammatory disorders (N = 4; 2 with pancreatitis that preceded onset of TMA and 1 each with nephrolithiasis and Stevens Johnson syndrome). Complement gene variants were present in 63.6% (14 of 22 patients with sequencing data available). The majority (59.3%) received plasma exchange before initiating eculizumab. Factor H autoantibody was detected in only 1 patient (of 22 tested). This patient (patient 57 in Figure 3) also had a compound heterozygous deletion of *CFHR3-CFHR1* and *CFHR1-CFHR4* (resulting in a homozygous *CFHR1* deletion), as well as a variant of undetermined significance in C3. Median time from presentation to eculizumab therapy was 2 (IQR: 2, 5) days. Median follow-up of the cohort was 27 (IQR: 5, 50) months. Table 1 summarizes demographics and clinical characteristics of the cohort at initial presentation.

Outcomes of eculizumab discontinuation

Of the 31 patients followed after receiving eculizumab for an acute episode of aHUS, 25 (80.6%) discontinued complement inhibition therapy (Figure 2) after a median duration on therapy of 2.37 (IQR: 1.06, 9.70) months. Six (19.4%) patients continued eculizumab. Of the 25 patients that discontinued eculizumab, 18 (72%) discontinued under physician direction (17 per protocol because of TMA remission including 2 with no renal recovery and end-stage renal disease and 1 because of nonresponse and a metabolic TMA thought more likely). Seven (28%) patients interrupted or discontinued therapy because of nonadherence. Reasons for continuing

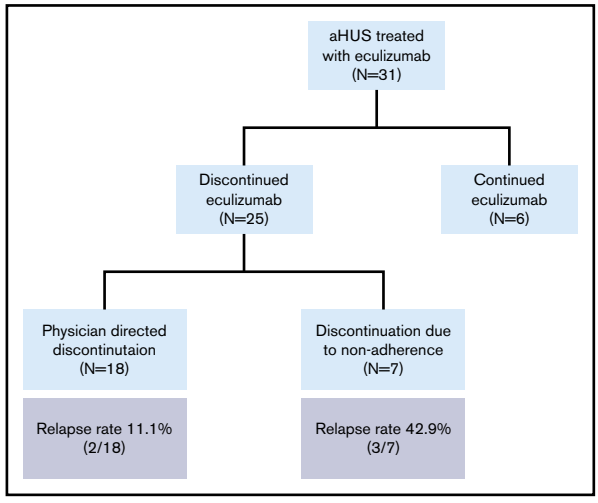

Figure 2. Cohort diagram.

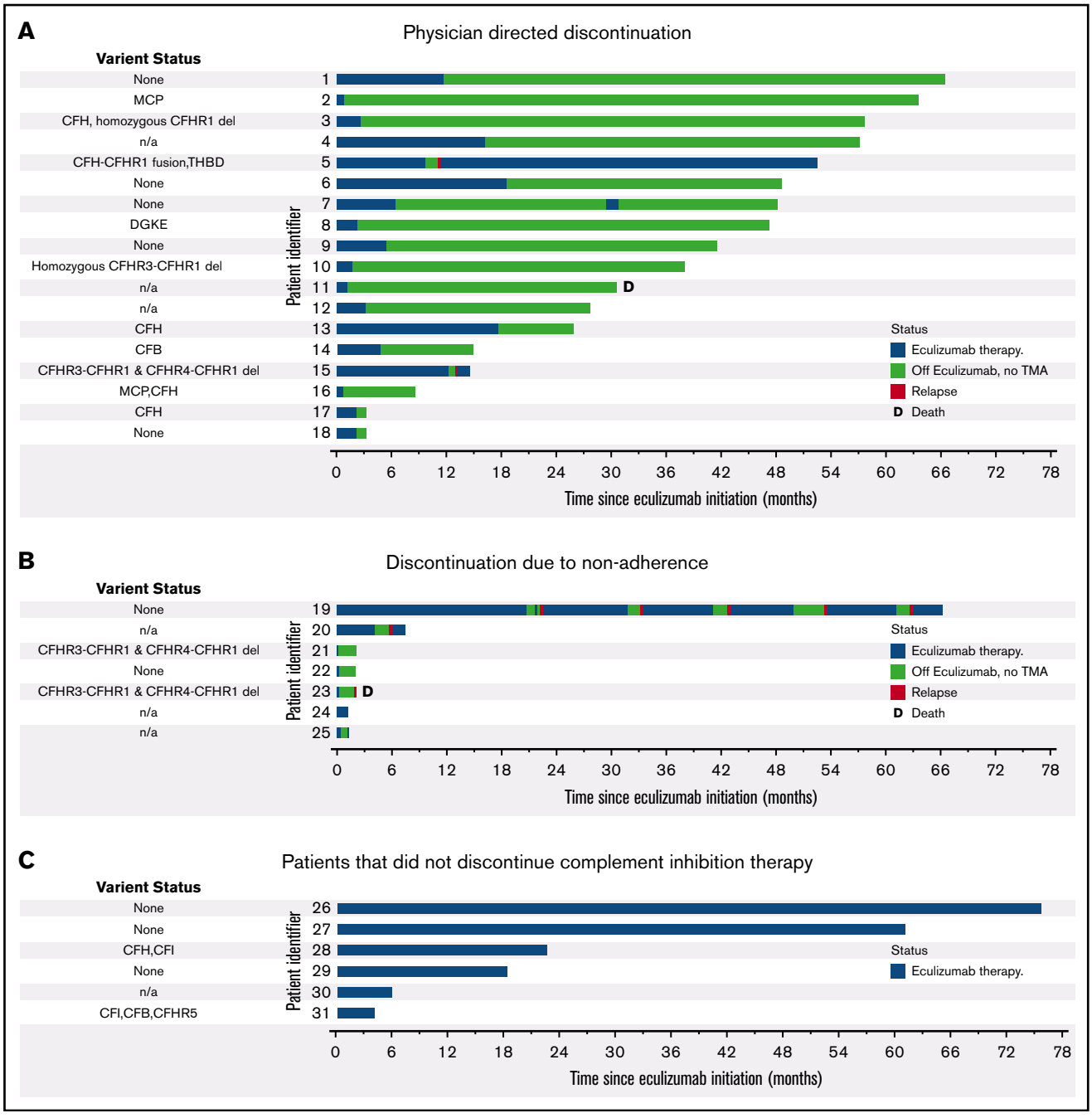

Figure 3. Clinical course after eculizumab cessation. (A) Patients that discontinued eculizumab on the physician-directed protocol. (B) Patients that discontinued or interrupted therapy due to nonadherence. (C) Patients that did not discontinue complement inhibition therapy. Origin of the x-axis is at initiation of eculizumab therapy for acute thrombotic microangiopathy. Duration of eculizumab therapy is indicated in blue, relapse is indicated in red, and relapse-free time off eculizumab therapy is indicated in green. Patient 23 (A) was briefly restarted on eculizumab in the setting of renal transplant. Patient 32 has switched to ravulizumab, and patients 51 and 55 are in the process of switching. D, death during follow-up.

eculizumab therapy included patient preference (N = 3), ongoing or recurrent trigger/inflammation (N = 2), and ongoing evaluation of underlying etiology (N = 1). Three patients have switched or are in the process of switching to ravulizumab (patients 32, 51, and 55 in Figure 2). No significant differences were noted in patients who discontinued vs continued complement inhibition therapy (Table 1).

Relapse occurred in 5 patients after stopping eculizumab, of which 3 were nonadherent with therapy and 2 had stopped under the treating physician's direction and monitoring. Thus, the overall relapse rate was 20.0% (5 of 25); however, the relapse rate was higher in the case of nonadherence vs a physician-directed cessation protocol (42.9% vs 11.1%, $P = .074$), although this did not reach statistical significance. One patient (patient 23 in

Table 1. Demographic and clinical characteristics at presentation by eculizumab discontinuation status

Variable	Total cohort (N = 31)	Continued eculizumab (n = 6)	Stopped eculizumab (n = 25)	*P*
Age, median (IQR), y	44 (25, 53.5)	32 (25, 48)	44 (32, 52)	.408
Female sex	80.6	66.6	80	.483
Race: White	64.5	83.3	60	.283
Race: African American	35.5	16.7	40	
Clinical presentation				
Neurologic				
Seizure	12.9	0	16.0	.294
Vision loss	12.9	33.3	8.0	.096
Unconsciousness	6.5	0	8.0	.474
Headache	38.7	66.6	32.0	.117
Encephalopathy	19.4	0	24.0	.181
Stroke	9.7	0	12.0	.372
Gastrointestinal				
Hemorrhage	3.2	0	4.0	.618
Epigastric pain	12.9	33.3	8.0	.096
Pancreatitis	9.7	0	12.0	.372
Transaminitis	12.9	16.7	12.0	.759
Vomiting	45.2	66.7	40.0	.239
Ischemic hepatitis	3.2	0	4.0	.618
Abdominal pain	38.7	33.3	40.0	.763
Respiratory				
Pulmonary edema	9.7	0	12.0	.372
Pleural effusion	6.5	16.7	4.0	.257
Other respiratory failure	12.9	0	16.0	.294
New or worsening hypertension	41.9	50	40	.655
Laboratory studies at presentation				
Hemoglobin, median (IQR), mg/dL	8.8 (7.6, 9.8)	9.1(8.3, 9.5)	8.8 (7.4, 10.1)	.673
Platelet count, median (IQR), $\times 10^9$/L	42 (18, 73)	33 (13, 41)	45 (19, 84)	.267
Serum creatinine, median (IQR), mg/dL	3.5 (2.8, 6.2)	2.7 (5.5, 9.0)	3.5 (2.9, 6.1)	.610
Lactate dehydrogenase, median (IQR), U/L	1329 (858, 2545)	5571 (3240, 6870)	1282 (800, 2501)	.036
Trigger identified*	67.7	66.6	68.0	.950
Complement variant present (n = 22 sequenced), % (n/N)	63.6 (14/22)	60 (3/5)	64.7 (11/17)	.743
Treatments				
Plasma exchange received	58.1	83.3	52.0	.162
Time to starting eculizumab, median (IQR), d	2 (2, 5)	2.5 (2, 5)	4 (2,5)	.487

Data are percentages unless otherwise noted.
*Triggers included infections (n = 7), autoimmune disease flares (n = 4), pregnancy and cesarean section (n = 1), surgery (n = 1), cancer/chemotherapy (n = 4), and other inflammatory disorders (n = 4).

Figure 3) who did not have a relapse reinitiated eculizumab in the peritransplant setting. Of the 5 patients that relapsed, 4 were re-treated and successfully salvaged with eculizumab and achieved remission without a decline in renal function (compared with renal function on the date of stopping eculizumab). One patient (patient 43) died after presenting to the emergency room at another institution with a diagnosis of recurrent TMA and hypertensive emergency in the setting of nonadherence to eculizumab and antihypertensive therapy. Another patient (patient 30) presented with altered mental status, cardiogenic shock, and multiorgan failure along with thrombocytopenia in the setting of refractory B-cell lymphoma 64 months after stopping eculizumab. He was treated with plasma exchange, followed by eculizumab for a possible TMA recurrence, but the family pursued comfort measures because of the poor prognosis of his malignancy and neurologic injury.

We examined factors associated with relapse. On univariate analysis, nonadherence with therapy (odds ratio [OR], 8.25; 95% confidence interval [CI], 1.02-66.19; $P = .047$) was associated with

Figure 4. Change in eGFR categories from date of stopping eculizumab until end of follow-up. Data from 25 patients that discontinued eculizumab presented as n (%). eGFR categories are shown in milliliters per minute per 1.73 m^2. Green cells represent improvement from baseline to day 183, red cells represent worsening, and white cells represent no change.

eGFR categories at stopping eculizumab (ml/min per 1.73 m^2) (N=25)		**eGFR categories at end of follow up** (ml/min per 1.73 m^2)					
		1 (>90)	2 (60-89)	3a (45-59)	3b (30-44)	4 (15-29)	5 (<15)
1 (>90)	4 (16%)	4 (16%)					
2 (60-89)	3 (12%)		3 (12%)				
3a (45-59)	5 (20%)		2 (8%)	3 (12%)			
3b (30-44)	3 (12%)		1 (4%)	1 (4%)		1 (4%)	
4 (15-29)	5 (20%)		2 (8%)		1 (4%)	2 (8%)	
5 (<15)	5 (20%)				1 (4%)	1 (4%)	3 (12%)
Total	25	4 (16%)	8 (32%)	4 (16%)	2 (8%)	4 (16%)	3 (12%)

relapse, whereas underlying complement gene variant (OR, 1.39; 95% CI, 0.39-4.87; $P = .598$) and the presence/absence of a trigger for aHUS (OR, 0.66; 95% CI, 0.09-4.79; $P = .687$) were not significantly associated with relapse. These analyses are limited by the small sample size and limited number of events (5 relapses), which also precluded multivariable regression analysis. Based on previous studies that found that *CFH* and *MCP* mutations were associated with relapse on discontinuing therapy,[15,22] we examined relapse rates in patients with *CFH* or *MCP* variants (40%, 2 of 5), other variants (33.3%, 2 of 6), no variants (0%, 0 of 6), and sequencing not completed (11.1%, 1 of 9; $P = .217$). Of note, 2 patients with *CFH* variants, 1 with other variants (*CFI*, *CFB*, and *CFHR5*), 2 without variants, and 1 who had not undergone sequencing continued on eculizumab and were excluded from the population at risk for relapse.

Renal outcomes after eculizumab discontinuation

Among the patients that discontinued eculizumab, there was no significant decline in mean eGFR from the date of stopping eculizumab (47.1 ± 28.2 mL/min per 1.73 m^2) until most recent follow-up (57.0 ± 28.0 mL/min per 1.73 m^2; 1-sided *t* test, $P = .987$). As shown in Figure 4, improvement in eGFR (defined by change to lesser stage of chronic kidney disease between stopping eculizumab and end of follow-up) was seen in 9 of 25 patients (36%), and stable eGFR (no change in stage of chronic kidney disease) was seen in 15 of 25 patients (60%). One patient (4%) had a decline in eGFR at the end of follow-up. The mean change in eGFR at the end of follow-up was not significantly different for patients that relapsed vs those that did not relapse (5.5 ± 12.0 vs 10.8 ± 20.5 mL/min per 1.73 m^2, $P = .625$) or between patients that stopped eculizumab because of nonadherence (with or without subsequent relapse) vs those that stopped eculizumab on the clinician-directed protocol (16.8 ± 23.0 vs 7.3 ± 17.5 mL/min per 1.73 m^2, $P = .305$).

Discussion

Our single-center experience demonstrates eculizumab discontinuation with close monitoring is safe in most patients with aHUS (with native kidneys), with low rates of TMA recurrence and effective salvage with eculizumab retreatment in the event of a recurrence. We also propose a protocol for discontinuation of complement inhibitory therapy and monitoring for recurrence (Figure 1).

Other studies have reported outcomes of eculizumab discontinuation in small cohorts of patients with aHUS, with median time on treatment before discontinuation ranging from 3 to 17.5 months (Table 2).[9-16] Recurrent TMA occurred in 20% to 30%, and retreatment with eculizumab led to remission, without progressive loss in renal function in most patients, although a recent observational study including patients from 5 parent eculizumab trials reported a decline in renal function in 40% of patients that stopped eculizumab.[13] The rate of recurrent TMA in our study was slightly lower (20%) than that reported previously. One reason for this may be the fewer number of patients in our cohort with *CFH* variants, which are associated with higher risk of relapse. Another possible explanation is most patients in our cohort stopped eculizumab while in remission from TMA and were monitored closely, whereas other cohorts have variable numbers of patients that discontinued or interrupted therapy because of nonadherence. In fact, nonadherence with therapy and monitoring were associated with a nearly fourfold higher rate of relapse in our cohort and were associated with the only aHUS relapse that led to worsening renal function and death.

Limited experience suggests that pathogenic variants in *CFH* may be associated with increased risk of aHUS recurrence off therapy.[9-11] In a retrospective analysis of 38 patients from the French aHUS registry, recurrence rates after eculizumab discontinuation were higher in patients with rare variants in *CFH* (72%) or *MCP* (50%) genes vs those without complement gene variants (0%).[22] In our cohort, the 6 patients without complement gene variants did not relapse, although the presence of rare complement gene variants was not associated with a statistically significantly higher risk of recurrent aHUS. Although not statistically significant, 40% of patients with *CFH* or *MCP* variants relapsed after discontinuing therapy compared with 33.3% of patients with variants other than *CFH* and *MCP*. These findings, however, may be because of the relatively small number of patients and relapses.

Table 2. Published series of eculizumab discontinuation in aHUS

Series	n	Median duration of therapy (range or IQR), mo	Median follow-up (since cessation) (mo)	Relapse rate, n (%)	Outcome of relapses
Ardissino et al[10] (Italy)	16	4.3 (0.5-14.4)	13.1 (1.2-28.2)	5 (31.3)	Retreated with eculizumab, no progressive renal injury
Sheerin et al[9] (UK)	14	—	—	3 (21.4)	Retreated without chronic sequelae
Wijnsma et al[15] (Netherlands)	17	3.8 (2.8-5.8)	27.4 (7.8-42)	5 (29.4)	Retreated with eculizumab, no progressive renal injury
Fakhouri et al[22] (France)	38	17.5 (2-50)	22 (5-43)	12 (31.6)	Eculizumab resumed with no significant change in GFR
Menne et al [13]	42	19.6 (0.2-86.9)	—	11 (26.1)*	40% had a decline in renal function after discontinuing but eGFR remained >60 mL/min/1.73 m^2
Fakhouri et al[16] (France)	55	Mean 16.5 (0.95, 59)	24	13 (23)	11 of 13 regained baseline renal function
Current study	25	2.4 (IQR 1.1, 9.7)	27 (IQR 5, 50)	5 (20)	Four salvaged with prompt eculizumab therapy. One patient died during recurrent TMA (nonadherent with therapy)

—, not reported.
*In this study, 21 (50%) restarted therapy for TMA relapse/renal impairment (n = 11), preparation for a kidney transplant (n = 5), short discontinuation period because of change in dose or missed doses (n = 2), administrative reasons (n = 2), and multiple serious adverse effects and a change in dosing (n = 1).

Despite these concerns, it is reassuring that relapsing patients with underlying variants were successfully retreated without a loss in renal function. Large prospective multicenter studies are needed to definitively establish the relationship between complement gene variants and risk of recurrent TMA after discontinuing complement inhibitory therapy. A major limitation is that robust functional data are available for few variants and in silico predictions are not uniformly reliable.[12,23,24] For the purpose of this study, we included all rare variants (minor allele frequency <0.005) regardless of functional assessment. There is increasing interest in identifying biomarkers of aHUS recurrence that would allow individualization of therapy. Unfortunately, serum complement assays such as C3, C4, C5b-9, AP50, or CH50 have not proved to be reliable biomarkers of disease activity for the diagnosis of aHUS[25-27] and are unlikely to be useful in monitoring for relapse off therapy. Functional assays such as the modified Ham assay[28] and assays looking at deposition of complement products on the endothelium have been developed and perform well in distinguishing aHUS from non–complement-mediated TMA.[29,30] These, however, are not available clinically, and their utility in monitoring still needs to be established. Finally, our cohort includes only adult patients with aHUS, and the applicability of our eculizumab discontinuation protocol should not be extrapolated to children with aHUS without evaluation in that population.

Other than relapse, long-term renal outcomes are a critical end point in studies evaluating restrictive eculizumab (or ravulizumab) strategies in complement-mediated TMA. At least 1 series reported a trend toward decreasing renal function over time from discontinuation.[13] Our relatively small cohort did not show a clinically significant decline in renal function after stopping eculizumab, which is concordant with previous reports. However, this needs to be established in large multicenter prospective studies. Finally, there is an established role of complement activation in atherosclerosis and coronary artery disease,[31] and variants in complement system genes *C3* and *MBL* are associated with cardiac disease.[32,33] Cardiovascular disease affecting the large- and medium-sized arteries has been reported even late in the course of aHUS.[34] It is plausible that ongoing subclinical complement activation, even if insufficient to cause overt TMA, may contribute to adverse cardiovascular outcomes. Long-term vascular outcomes of eculizumab cessation also need to be evaluated.

In summary, we show that for most aHUS patients, discontinuation of C5 inhibitor (eculizumab) therapy is safe and acceptable without loss in renal function when done under close monitoring to allow early detection and treatment of relapses. Multicenter, prospective studies are needed to establish the renal and vascular safety of limited duration eculizumab therapy for aHUS, which has the potential to reduce the financial burden, the inconvenience of frequent infusions, and the small but real risk of meningococcal infection associated with indefinite therapy with terminal complement inhibitors.

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Authorship

Contribution: S.C. collected data, designed and performed the analyses, interpreted the data, and wrote the first draft of the manuscript; N.D. and H.U. collected data; S.H. collected data and prepared figures; E.M.B., X.Y., C.J.S., A.R.M., and R.A.B. interpreted the data and critically reviewed the manuscript; and all authors critically reviewed the manuscript and approved the final version.

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ORCID profiles: S.C., 0000-0001-6832-2389; X.Y., 0000-0002-7304-9927; C.J.S., 0000-0002-8409-0714; A.R.M., 0000-0002-8673-4317.

Correspondence: Shruti Chaturvedi, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross Research Building, Room 1025, Baltimore, MD 21205; e-mail: schatur3@jhmi.edu.

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